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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAKH, YELENA G	
ART UNIT	**PAPER NUMBER**
1743	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,884	BERLIN ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-30 and 33-39* is/are pending in the application.

4a) Of the above claim(s) *15-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/15/04, 01/31/05*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

1. Amendment filed 05/23/05 is acknowledged. Claims 15-30 and 33-39 are pending in the application, of which claims 15-30 are withdrawn from consideration on merits.

Response to Amendment

2. Objection to the drawings and specification remains. Rejections of the pending claims are modified in light of the amendment. Rejection of the pending claims over the prior art is withdrawn at this stage of the prosecution, since the issues of enablement of the pending claims are not answered in the amendment. The specification does not provide any working examples for the method claimed in the instant application.

Information Disclosure Statement

3. The Applicants appear to present the same references in IDS twice. The examiner would like to request the Applicants to carefully consider all previously submitted IDS in order to avoid confusion in handling the application.

Double Patenting

4. Claims 33-39 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 31-37 of copending Application No. 10/262,349. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Drawings

5. The drawings are objected to because:

a, Figure 1 shows incorrect method steps. While the step of irradiating sample is an active step of the method, the step of scattering radiation from the sample is not, since scattering

radiation is an intrinsic feature of the sample. Also, the step of resonating scattered radiation can follow the step of scattering the radiation only if the sample is placed into or close to a resonance cavity, which should occur before the experiment starts. The step of "irradiating scattered radiation from the chamber" is completely unclear, as it will be discussed further.

b, Figure 2 should be designated by a legend such as --Prior Art-- because only that which is old is illustrated. See MPEP § 608.02(g). Corrected drawings in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Further, description of Figure 2 in the specification on page 7 reciting "an aqueous solution of a diluted nucleic acid derivative" should be rewritten as "a diluted aqueous solution of a nucleic acid derivative", since it is the solution that is diluted, rather than a DNA derivative. Also, Figure 2 should demonstrate the means, which separate just one molecule from such diluted solution to place it in the chamber 250 to have the sample disclosed in the specification and claims, i.e. the sample comprising just one molecule. No such means are shown on the Figure. The specification discloses a resonance cavity in the analysis chamber into which a molecule should be placed in order to perform the method disclosed, which basically coincides with the analysis chamber except for the mirrors. Again, it is not clear from the drawing, how a single molecule is held in the cavity during the analysis. Especially it is not clear, how the sample can be flowed continuously into the chamber, if the sample is supposed to contain just one molecule. From the specification it appears that the resonance cavity is a required feature of the system for performing the method disclosed, which means that it should be indicated separately on Figure 2. Moreover, its structure is predetermined by several parameters, including the resonance frequency and the frequency of the detected radiation. This requires preliminary analysis of the same analytes in order to obtain these frequencies. Only then the enabled structure depicted on Figure 2 can be constructed. The specific relations between the cavity height and analyte frequencies need to be indicated on the Figure.

c, Figure 4 is referred to as representing Stokes Raman spectra of diluted samples of four DNA nucleotides "according to embodiments of the invention". Which embodiments are meant here? The invention is supposed to be directed toward stimulated enhanced Raman spectroscopy, while Figure 4 demonstrates spontaneous Raman spectra, performed by a standard Raman technique. It is not clear, which inventive features of which embodiments are meant in the above expression.

Specification

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The specification is objected to as not containing "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art" to practice the method in its best mode.

The specification appears to be a mix of discussion of the prior art and well-known theoretical concepts of various forms of Raman spectroscopy along with disclosing possible structures of resonant chambers for different Raman techniques based on these theoretical concepts. According to the specification the chambers can be adapted for analysis of plural molecules and single molecules, including nucleotides of DNA. However, no ways of preparing samples containing single molecules of DNA (not mentioning single molecules of nucleotides) are disclosed in the specification, which makes it unclear, on how such samples can be prepared. The only real experiments represented in the specification refer to standard spontaneous Raman spectroscopy of four nucleotides, which cannot be considered inventive features of the method, since this technique is well known in the art.

The language and structure of the specification disclosing variety of possible embodiments of Raman techniques along with the resonance chambers together with known methods of the prior art makes it difficult to understand the inventive features of the method and system disclosed. The definition "resonance enhanced stimulated Raman spectroscopy" is not represented in such clear terms so as to differentiate it from stimulated "surface-enhanced

resonance Raman scattering" (SERRS), the application of which for detection of single DNA molecules is also well known and documented (see e.g. Graham et al., Anal. Chem., 1997). The same is true for the definition of "resonant spectroscopic analysis chamber", which is not clear from the specification. Referring to Figure 15 (page 3), which "shows an exemplary apparatus and method for nucleic acid sequencing" by all possible Raman spectroscopy techniques, i.e. SERS, SERRS, CARS, and "resonance enhanced Raman spectroscopy" raises a question of how can all these different methods be performed with the same apparatus?

On page 6, line 10, the disclosure reads "irradiating or transmitting the scattered radiation from the chamber". While the term "transmitting" in "transmitting the scattered radiation from the chamber" can be easily understood, it is not clear, what "irradiating the scattered radiation" might be. According to Merriam-Webster On-Line Dictionary, "irradiate" means "to cast rays of light upon" or "to affect or treat by radiant energy (as heat); *specifically* : to treat by exposure to radiation". It is not apparent what is meant by the expression "irradiating the radiation".

It seems that constructing the inventive spectroscopic system for performing the claimed method depicted on Figures 5 and 6 requires preliminary knowledge of exactly the same parameters that are supposed to be obtained by the method, e.g. "a wavelength of an inelastically scattered radiation of a molecule of interest" (page 16). This makes it unapparent how such system can be constructed.

It is unclear, if coherent anti-Stokes Raman spectroscopy (CARS) for detecting a single molecule requires a specific device or specific experiment set-up. What is disclosed on page 25 is a conventional CARS.

Furthermore, the only other examples of real Raman experiments shown on Figures 16-21 refer to SERS technique, which is well known and documented as the method for detecting single DNA molecules. The examples make it unclear, if SERS is considered one of the embodiments of the instant method. Figure 4 refers to "Stokes Raman spectra for dilute aqueous solutions of four DNA nucleotides, according to embodiments of the invention". However, it is not clear, which specific embodiments are meant here, and hence which specific Raman spectroscopy experiments Figure 4 illustrates.

Thus, it is not clear, which specific inventive features of Raman spectroscopy are disclosed in the specification, and which specific devices are required for performing different Raman techniques.

In conclusion, the specification is written in such a vague language regarding the inventive features of methods and apparatus for detecting single molecules by Raman spectroscopy, that it is difficult to apprehend the essence of the invention.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide an adequate disclosure for the claimed invention, since it is not clear, how it is possible to selectively resonate inelastically scattered radiation of different molecules in the chamber; how the molecules are held in the chamber; how the selectively enhanced resonance can be selectively transmitted? If the chamber resonates at several close frequencies, all resonances will be enhanced. How is it possible to selectively resonate one, and then selectively resonate another in the same chamber? Moreover, the second step of the method requires constructing the resonance chamber according to the resonance frequencies of the molecules to be analyzed. How different can be the resonance frequencies to construct such chamber? Why irradiating the sample at a certain frequency will not lead to resonating all frequencies of all molecules if they have close resonance frequencies? The specification does not disclose any working examples of such experiments.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Clam 36 "selectively resonating inelastically scattered radiation characteristic". It is not apparent, how it is possible to resonate a characteristic. Moreover, it is not clear, how it is possible 'to create a selective resonance at the characteristic resonance frequency of the molecule' (if this is what is meant in the claim's recitation), if the target molecules are different. What is meant by the word "resonating" here? If resonating occurs because of the resonance provided by the resonance cavity at a specific frequency, then it is an intrinsic feature of the resonance cavity, and not an active step of the method. It is completely unclear, how it is possible to get such resonance at the first frequency and then at the second frequency from the same resonance cavity? Does it depend on the irradiating the sample at different frequencies? How such selectivity of the resonance can be achieved, if the resonance parameters are characteristics of the resonance cavity?

Claim 37 recites "selectively resonating inelastically scattered radiation characteristic of an average wavelength". Besides having the same technical problems of incorrect language, the claim is unclear as to what is recites. How is it possible to "selectively resonate" at an average wavelength? What active step is required for this? While irradiating the sample can be considered an active step of the method, resonating is a specific feature of the resonance cavity, and is defined by its specific characteristics. Therefore, it is completely unclear as to what is meant by the expression "selectively resonating".

What is the step of "optionally identifying a particular derivative"? First, if there is no identification of such derivative, than it is not clear as to what the method is directed to. Detecting the transmitted radiation? What would be the sense of such method? On the other hand, if such identification occurs, it is not clear, how it is performed. By comparing the resultant frequency with all possible resonance frequencies of all possible molecules in the set of molecules?

Response to Arguments

10. Applicant's arguments filed 05/23/05 have been fully considered but they are not persuasive. Objection to Drawings. Applicants express their position regarding drawings as the following: 'the illustrations provided in the instant application are provided to "facilitate an understanding of the invention" '. Unfortunately, rather than "facilitate an understanding of the invention" the illustrations confuse it even more. The examiner does not indicate in the Office action that the drawings must be presented in order to disclose the invention. However, if they are presented, they have to clearly and unambiguously indicate all the novel features of the invention, which the drawings of the present application fail to do. Figure 1 presents a chart with unclear and indefinite method steps. Figure 2 does not represent anything new, and therefore should be labeled -- Prior Art --; **see MPEP § 608.02(g)**. If the Applicants do not agree with such interpretation, the novel features of the scheme represented by Figure 2 should be clearly indicated in the drawing and discussed in the specification.

Regarding detection of a single molecule in the optical resonance chamber. The examiner would like the Applicants to indicate specifically, which examples refer to obtaining *resonance enhanced* spectra using *resonance chamber* of the invention, rather than obtaining *SERS* spectra using *nanoparticles*, which are well known in the art. As far as the examiner understands from the specification, Figure 22 refers to simulation of the curves from hypothetical experiments. If the examiner is mistaken in her interpretation, she kindly requests the Applicants to indicate, where in the specification the Applicants provide experimental data related to the disclosure of the invention, rather than experiments known in the art or simulated data. Attaching a single DNA molecule to a nanoparticle is not the same as placing it for a definite time into the resonance cavity of the resonance chamber. The examiner is not convinced by the Applicants' remarks as to how this was done in the instant case.

Regarding presenting specific features of the invention in the drawings. The examiner cannot agree again with the Applicants' position that the drawings should not present novel features of the invention. If the novel features are essential for practicing the invention, they should be presented in the drawings for clarification purposes. The drawings of Figures 5 and 6 are so schematic that it is not really clear, where the molecule is placed during the experiment

and how it can be held there. Again, as it was indicated above the Applicants only demonstrated using nanoparticles, which themselves provide surface-enhanced Raman spectra. The Examiner failed to find any other experiments, which would use the resonance chamber of the present invention for obtaining resonance enhanced Raman spectra.

Regarding drawing 4. The Applicants explain that Figure 4 represents Raman spectra of different nucleotides, which has "the impact ... on the design of a resonance chamber of the invention". If the spectra are known in the art, the drawing should be labeled -- Prior Art --, as it was discussed above. If Figures 16-21 demonstrate resonance enhanced Raman spectra obtained by using the resonance chambers of the instant invention, it should be clearly indicated in the specification, which is not done now. It seems to the examiner that what is shown in the Figures are SERS spectra of nucleotides obtained by using nanoparticles. If this is different from what examiner assumes, she would appreciate the Applicants' explanation.

Objection to the specification. The examiner properly identified, what is objected to in the *specification*, rather than the pending claims. The specification does not include claims, which were the issue of a separate examination and rejection. Therefore, objection to the specification should not include rejection of the claims under the same paragraph. The examiner made it quite clear of why the issue of non-clarity and indefiniteness of the specification was raised in the previous Office action. The examiner objects to the specification as not complaining with the requirements of 35 U.S.C. 112, first paragraph regarding a "full, clear, concise, and exact" description of the invention. The examiner believes that enough examples of unclarity of the description were provided in order to object the specification as not being written in compliance with the requirements of first paragraph of 35 U.S.C. 112.

Regarding the enablement of the invention. In order for the Applicants to demonstrate that the method of the instant application is enabled, they should provide at least one working example related to the invention, i.e. the method of obtaining resonance enhanced Raman spectra using the novel resonance chamber. So far, the examiner failed to find such example, as the spectra demonstrated on Fig. 4 are the Raman spectra well known in the art, and the spectra shown on Figures 16-21 seem to be obtained using nanoparticles. If this interpretation is incorrect, the examiner respectfully requests enlightening the Applicants' position.

Regarding rejection of the claims under 35 U.S.C. 112, first paragraph. The Applicants refer to paragraph [0048] (rather than [0047], as written in the excerpt). The whole paragraph is written in the language of various possibilities, related specifically to the design of the resonance chamber. From the paragraph it follows that to design the desired resonance chamber not only the target molecule should be known, its specific Raman spectral characteristics should be known, on the basis of which the resonance chamber "may be" designed so that to detect the desired molecule. It looks like in the case the molecule is not there, another resonance chamber should be designed for another desired molecule so that the molecule can be detected in the sample, if it is there. In the case of a plurality of molecules, which should be the difference between their resonance frequencies so that the resonance chamber would enhance their resonances? Will they all be enhanced simultaneously? The examiner does not consider the paragraph as containing enough information for enabling one skilled in the art to make and use the claimed invention. Also, the examiner did not find any working examples related specifically to using the resonance chamber of the instant application.

Rejections of the pending claims under 35 U.S.C. 112, first paragraph are changed in view of the amendment.

The examiner does not apply any prior art to the amended claims, which do not seem to be enabled by the specification at the present time.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

7/10/05

Yelena Gakh

YELENA GAKH
PRIMARY EXAMINER